

A166280

AD-A166 280

DNA-TR-85-50

NUCLEAR WEAPON EFFECT RESEARCH AT PSR—1983

~~CONFIDENTIAL~~—Symptomatology of Acute Radiation Effects in Humans
after Exposure to Doses of 75 to 4500 Rads (cGy) Free-In-Air

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31 August 1984

Technical Report

CONTRACT No. DNA 001-83-C-0015

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Nuclear Weapon Effect Research at PST-1983 ~~W-11-11-11~~ Symptomatology
of Acute Radiation Effects in Humans after Exposure to Doses
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SECURITY CLASSIFICATION OF THIS PAGE

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188
Exp. Date: Jun 30, 1986

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED		1b. RESTRICTIVE MARKINGS	
2a. SECURITY CLASSIFICATION AUTHORITY		3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution is unlimited.	
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE N/A since UNCLASSIFIED		5. MONITORING ORGANIZATION REPORT NUMBER(S) DNA-TR-85-50	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) PSR Report 1422		7a. NAME OF MONITORING ORGANIZATION Director Defense Nuclear Agency	
6a. NAME OF PERFORMING ORGANIZATION Pacific-Sierra Research Corporation	6b. OFFICE SYMBOL (If applicable)	7b. ADDRESS (City, State, and ZIP Code) Washington, DC 20305-1000	
6c. ADDRESS (City, State, and ZIP Code) 12340 Santa Monica Boulevard Los Angeles, CA 90025-2587		9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DNA 001-83-C-0015	
8a. NAME OF FUNDING/SPONSORING ORGANIZATION	8b. OFFICE SYMBOL (If applicable)	10. SOURCE OF FUNDING NUMBERS	
8c. ADDRESS (City, State, and ZIP Code)		PROGRAM ELEMENT NO 62715H	PROJECT NO P99QAXD
		TASK NO B	WORK UNIT ACCESSION NO DH006427
11. TITLE (Include Security Classification) NUCLEAR WEAPON EFFECT RESEARCH AT PSR-1983 Effects in Humans after Exposure to Doses of 75 to 4500 Rads (cGy) Free-In-Air Symptomatology of Acute Radiation Effects in Humans after Exposure to Doses of 75 to 4500 Rads (cGy) Free-In-Air			
12. PERSONAL AUTHOR(S) Siegmond J. Raum Robert W. Young		George H. Anno H. Rodney Withers	
13a. TYPE OF REPORT Technical	13b. TIME COVERED FROM 821027 TO 831130	14. DATE OF REPORT (Year, Month, Day) 840831	15. PAGE COUNT 70
16. SUPPLEMENTARY NOTATION This work was sponsored by the Defense Nuclear Agency under RDT&E RMSS Code B350083466 P99QAXDB00200 H2590D.			
17. COSATI CODES		18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)	
FIELD	GROUP	SUB-GROUP	
6	18	Lethal Dosage, Nuclear Effects, Nuclear Radiation, Nuclear Accidents, Radiation Sickness, Symptomatology, Radiation Therapy, Radiation Effects, Ionizing Radiation.	
19. ABSTRACT (Continue on reverse if necessary and identify by block number) This report distills from available data descriptions of typical human symptoms in reaction to prompt ionizing radiation in the dose range 75 to 4500 rads (cGy) free-in-air. The descriptions correlate symptoms with dose and time over the acute postexposure period of six weeks. Their purpose is to provide an empirical base for estimating combat troop performance after a nuclear weapon attack. We divide the dose range of interest into eight subranges associated with important pathophysiological events. For each subrange, we estimate the signs and symptoms manifested by an exposed population--symptom onset, severity, duration, and incidence. The early or prodromal phase of radiation sickness begins about 2 to 4 hrs after doses of 300 to 530 rads (cGy). Onset time diminishes with dose, occurring within minutes of exposure to 4500 rads (cGy). Characteristic prodromal symptoms are nausea, vomiting, anorexia, and diarrhea. The prodromal phase lasts from several days to a matter of hours, depending on dose.			
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT <input type="checkbox"/> DTIC USERS		21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED	
22a. NAME OF RESPONSIBLE INDIVIDUAL Betty L. Fox		22b. TELEPHONE (Include Area Code) (202) 325-7042	22c. OFFICE SYMBOL DNA/STT1

18. SUBJECT TERMS (Continued)

Cont. → Radiobiology, Signs and Symptoms
Radiation Injury, Radiation Dosage ←

19. ABSTRACT (Continued)

Cont. The delayed or manifest-illness phase begins weeks to days after exposure, onset time diminishing with increasing dose. Symptoms result primarily from injury to the hemopoietic system at doses of 150 to 1500 rads (cGy), and injury to the gastrointestinal system at doses above 1500 rads (cGy). Compound effects from both syndromes are manifested at doses of 830 to 1500 rads (cGy). Symptoms of the hemopoietic syndrome are bleeding, fever, infection, and ulceration. Symptoms of the gastrointestinal syndrome are fluid loss, electrolyte imbalance, severe diarrhea, and septicemia.

Despite differences of population characteristics, environmental conditions, and medical attention between the exposed persons represented by our data and battlefield soldiers, we believe these symptom descriptions are relevant to combat personnel. Keywords:

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SUMMARY

As a first step toward estimating combat troop performance after the detonation of nuclear weapons, this report describes typical human symptoms in response to prompt ionizing radiation during the acute period of six weeks after exposure.

Data on human radiation sickness symptoms are both diverse and sparse. They consist of (1) case studies of the victims of nuclear reactor accidents, (2) records of patients given radiation therapy for cancer and other diseases, (3) analyses of "composite" data, including the experience of Japanese atomic bomb survivors, and (4) expert opinion. Rather than restating the well-known variability of radiation sickness symptoms, the literature has been analyzed to reach a consensus about *typical* symptoms.

The intermediate dose range of interest, 75 to 4500 rads (cGy) free-in-air, was divided into eight subranges associated with important pathophysiological events. For each subrange, the signs and symptoms manifested by an exposed population--their onset, severity, duration, and incidence--were estimated.

The acute period of radiation response has two pathophysiological phases: an early prodromal phase and later manifest-illness phase. The prodromal phase begins about 2 to 4 hr after doses of 300 to 530 rads (cGy), and earlier with increasing dose down to minutes after exposure to 4500 rads (cGy). The characteristic signs and symptoms are nausea, vomiting, anorexia, and to a lesser degree diarrhea. Beginning at doses of about 530 rads (cGy), and as vomiting and diarrhea become severe, fluid loss, electrolyte imbalance, and headache are manifested. The prodromal phase lasts from several days to a matter of hours, depending on the dose.

The manifest-illness phase begins weeks to days after exposure, onset time diminishing with increasing dose. Symptoms result primarily from injury to the hemopoietic system at doses of 150 to 1500 rads (cGy) and injury to the gastrointestinal system at doses above

1500 rads (cGy). Compound effects from both syndromes are manifested at doses of 830 to 1500 rads (cGy). Symptoms of the hemopoietic syndrome are related to bleeding and infections. They include easy bruising, fever, and ulceration of the mouth and throat. Systemic infections are triggered by the escape of enteric bacteria from the damaged gastrointestinal mucosa; they progress fast because white blood cell production is suppressed by the radiation-caused destruction of bone marrow stem cells. Preexisting infections, for example in the respiratory tract, can rapidly become lethal. With increasing dose, and especially above 1300 rads (cGy), fluid loss and electrolyte imbalance from vomiting and injury to the gastrointestinal tract may lead to fainting, prostration, and a shock condition that could result in death in ~2 to 12 days.

Application of these descriptions to battlefield soldiers carries some reservations because of differences in population characteristics, environmental conditions, and medical attention. Accident victims and therapy patients had the benefit of medical care, which battlefield soldiers may not have. On the other hand, soldiers would presumably have advantages of youth, vigor, and motivation over the other groups mentioned. The data do not permit a quantitative assessment of the tradeoffs between postexposure medical care and preexposure robustness. We believe, however, that preexposure health condition is less important than postexposure medical care, barring prior bacterial or viral infection. The symptom descriptions may be somewhat less applicable but still reasonably relevant to combat personnel receiving doses at the lower end of the 75 to 4500 rad (cGy) range or soon after exposure. The descriptions become increasingly applicable as doses and post-exposure time increase.

PREFACE

This report was prepared as one volume of a set comprising the Pacific-Sierra Research Corporation (PSR) final report for the Defense Nuclear Agency (DNA) under contract DNA001-83-C-0015. The work done under this contract spans a wide range of nuclear weapon effects research covering intermediate-dose radiation, cratering, fire research, analytical models, underground testing instrumentation, and microwave energy.

This report distills from available data descriptions of typical human symptoms in reaction to prompt ionizing radiation in the dose range 75 to 4500 rads (cGy) free-in-air. The descriptions correlate radiation sickness symptoms with dose and time over the acute post-exposure period of approximately six weeks.

The symptom descriptions are intended to provide a base for developing estimates of combat troop performance after the detonation of nuclear weapons. Such estimates, essential for military contingency planning, are the goal of the Intermediate Dose Program (IDP) of research sponsored by DNA. This work may also be of interest to policy officials and health care personnel responsible for civilian emergency management. Understanding of acute radiation effects aids planning for civil defense measures, medical facilities, and therapeutic procedures.

DNA staff members David L. Auton and Cyrus P. Knowles supervised the research, and the IDP Core Group provided advisory support. Related reports include:

George H. Anno, Harold L. Brode, and Ruth Washton-Brown, *Initial Human Response to Nuclear Radiation*, Pacific-Sierra Research Corporation, Note 477, April 1982 (subsequently published as DNA-TR-81-237 and Chap. II of PSR Report 1241).

George H. Anno, *Acute Radiation Response in Humans: Informal Comments by Physicians and Radiobiologists*, Pacific-Sierra Research Corporation, Note 492, rev. June 1983 (subsequently published as Vol. 14 of PSR Report 1317 and DNA-TR-82-179).

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SECTION 1

INTRODUCTION

According to U.S. Army criteria for the employment of combat units after a nuclear attack, a radiation dose of at least 3000 rads (cGy)* free-in-air[†] is required to render troops incapable of combat performance. Current scenarios suggest that for every soldier who receives an incapacitating radiation dose, another will receive a lethal but not incapacitating dose, 450 to 3000 rads (cGy). Two more soldiers will receive doses between "troop safety" and lethal levels, 50 to 450 rads (cGy). Many will show symptoms of radiation sickness and impaired ability to perform their normal combat tasks. The effectiveness of units manned by such sick and "walking dead" troops could become an important factor in the battlefield employment of nuclear weapons. With the continuing possibility that such weapons might be used, it is troubling that radiation-induced effects on combat performance remain poorly understood.

This is the first report of a research program intended to improve our ability to predict the degree of functional impairment in military units exposed to ionizing radiation.[‡]

For application to battlefield operations, the concern is with early radiation effects, those occurring within a few weeks of exposure. Because the effects of intermediate radiation doses are least well understood, the focus is on the dose range 75 to 4500 rads (cGy).

Given the lack of empirical data relating combat effectiveness to radiation exposure levels, a reasonable approach is to examine the symptoms** associated with radiation sickness and relate the symptoms to performance.

*One centigray (cGy) is equal to one rad.

[†]Unless stated otherwise, all dose levels are free-in-air values.

[‡]This research excludes blast and thermal radiation, the two other causes of injury from nuclear weapon detonation.

**Throughout this report, "symptoms" is used to mean both subjective evidence and objective signs of radiation sickness.

As a first step in that effort, this report describes the "typical" human response to prompt radiation during the acute period of 6 weeks after exposure. The available data has been analyzed to correlate radiation sickness symptoms with dose levels and time--incidence, severity, and duration. Rather than restate the well-known variability of radiation sickness symptoms, a typical description was derived to provide a theoretical base for subsequent estimates of combat troop performance after the detonation of nuclear weapons.

The data sources fall into four general categories: (1) case studies of the victims of nuclear reactor accidents,^{*} (2) records of patients given total-body radiation therapy for cancer and other diseases,[†] (3) "composite" analyses based on data from a variety of sources, and (4) expert opinion, sometimes elicited in private communication. Additional information has come from survivors of the atomic bombings in Hiroshima and Nagasaki, as well as those accidentally irradiated in nuclear tests in the South Pacific.[‡] Though animal experiments provide the greatest quantity of data on radiation effects,^{**} animal data was not relied on because the link with human responses is indirect.

No one category of sources provides a comprehensive picture of the incidence, severity, and duration of radiation sickness in humans. For example, the data on atomic bomb survivors are usable for delayed hematological effects (≥ 1 week postexposure) but inadequate for early acute effects; because of the chaotic conditions, all records of symptoms during the first few postexposure days were constructed some time after the fact.^{††} To refine a plausible description of acute symptoms, it is necessary to use a variety of sources and carefully evaluate their data.

^{*}References 12, 21, 45, 51, 53, 56-58, 73, 74, 83, 90, 94, 96, 103-105.

[†]References 2, 9, 10, 15, 17, 19, 20, 42, 43, 66, 71, 78, 88, 91, 93, 98.

[‡]References 2, 26-29, 54, 55, 60, 63, 65, 72, 81, 82, 101, 106, 108.

^{**}References 3, 5, 11, 13, 14, 100, 111.

^{††}References 81, 82.

Application of these data to battlefield soldiers naturally carries some reservations because of obvious differences in population characteristics, environmental conditions, and medical attention. Accident victims and therapy patients all had the benefit of medical care in varying degrees. Battlefield soldiers might well have no access to such care. The data do not permit a quantitative assessment of the effects of such differences, but they are addressed qualitatively.

Section 2 explains the parameters adopted and assumptions made for deriving a consensus on typical symptoms from the data. Section 3 presents our findings.

SECTION 2

ANALYTIC CONSIDERATIONS

This section explains how the data were used to correlate symptoms of radiation sickness with dose levels and time after exposure for a typical population of victims. The effort involved identifying the specific *symptom*, estimating their *incidence* and *severity* in the population, reconciling *dose levels* reported in different units of measure, correlating *dose ranges* and *time* intervals with symptoms, and addressing the effect of different *dose rates* in the data. The period of acute illness is conventionally divided into the prodromal phase (1 to 3 days after exposure) and manifest-illness phase (1 to 6 weeks after exposure).

IDENTIFICATION OF SYMPTOMS

The main prodromal symptoms identified are nausea, vomiting, anorexia, diarrhea, fluid loss, and electrolyte imbalance. Concomitant effects, either a direct result of radiation or secondary to fluid loss, are headaches, fainting, and prostration. Other early effects with a different pathophysiological base are fatigue and weakness.

The manifest-illness phase is dominated by bleeding, fever, infection, and ulceration due to injury of the hemopoietic system. Higher doses can produce hypotension, dizziness, and disorientation. Fluid loss, electrolyte imbalance, and delayed diarrhea recur after relatively high doses because of damage to the intestines.*

SYMPTOM INCIDENCE AND SEVERITY

Apart from probit analyses[†] and information on atomic bomb survivors, quantitative data on the incidence of symptoms are scanty. Analysis has indicated substantial divergence between the Japanese survivor data and probit analysis predictions of symptom incidence.[‡] The reason for the

*Appendix A explores the pathophysiological basis of both prodromal and manifest-illness symptoms.

[†]References 61, 67.

[‡]References 9, 63.

divergence is unclear. The probit data were used because they draw on more reliable accounts of accident victims and over 2000 therapy patients. However, even the probit data are not specifically correlated with post-exposure time, so the time dependence of symptom incidence has been approximated.

To express symptom severity, the terms used were "mild," "moderate," and "severe." This usage reflects common clinical distinctions, but we are unable to attach quantitative values to the terms for most of the symptoms identified above. Either the data do not permit quantification or quantification is inappropriate (for example, by what measure could one distinguish moderate from severe nausea or headaches?). In Sec. 3, quantitative links are shown where possible but the authors mainly rely on readers' qualitative understanding of the distinctions.

DOSE LEVELS

In this report radiation doses are expressed as free-in-air values, which are relevant to a radiation environment in the battlefield. However, most of the data sources, particularly the therapeutic accounts, express doses in midline tissue dose (MTD) values. For comparability in developing typical symptom descriptions, MTD values were adjusted, multiplying by 1.5 ($1/0.66$). The 0.66 factor suggested by Lushbaugh accounts for photon-dose attenuation from the surface of the body (free-in-air exposure dose) to the body midline.* The same multiplication factor was applied to estimate the free-in-air values where neutrons were present, roughly accounting for the combined first-collision neutron and secondary-photon absorbed dose at the center of the body.† This underestimates the free-in-air dose values converted from the accident data because of the mixed gamma and neutron radiation involved. For example, if an MTD neutron-gamma dose ratio of 1:3 (probably high for the accident data) is assumed, the underestimate is about 14 percent. Because of the broad dose ranges chosen (see below) and the uncertainty of the dose estimate in the accident data, that amount is insignificant for our

*References 67, 70.

†Reference 67.

analysis. Of course, no adjustment was necessary for the mixed gamma and neutron radiation doses to which accident victims were exposed when reported as free-in-air values.

More precise estimates require detailed consideration of radiation transport and dosimetry (involving spectra, geometry, and composition), which is beyond the scope of this research. We do not explicitly account for relative biological effectiveness (RBE). The data do not justify values other than 1, particularly for acute symptoms such as upper and lower gastrointestinal distress, fatigue, and weakness.

DOSE RANGES

We subdivided the dose range of consideration, 75 to 4500 rads (cGy), into eight ranges reflecting important pathophysiological events, as shown in Table 1. Doses in the lowest range, 75 to 150 rads (cGy), cause minor acute damage to the hemopoietic system and mild prodromal effects (nausea, vomiting, anorexia) in a small number of irradiated persons.

In the dose range 150 to 300 rads (cGy), prodromal effects and injury to the hemopoietic system (primarily the bone marrow stem and precursor cells) increase significantly. However, victims will probably survive, except for the ~2 to 5 percent who will die after doses of about 300 rads (cGy).^{*} The probability of death increases at this dose range if victims are already weakened by other conditions, such as an infection. Although survival is possible within the next range, 300 to 530 rads (cGy), prodromal effects become pronounced. Victims also suffer moderate to severe damage to the bone marrow. As the dose reaches about 500 rads (cGy), 50 percent who do not receive appropriate medical care may die within 60 days.[†]

The lower limit of the 530 to 830 rad (cGy) dose range is the estimated LD_{50/60}; 100 percent lethality is approached at about 750 rads (cGy).[‡] Responses to doses between 830 and 1100 rads (cGy) begin to

^{*}References 61, 75.

[†]Reference 61.

[‡]References 61, 77.

Table 1. Dose ranges and associated pathophysiological events.

Dose Range, rads (cGy)	Pathophysiological Events		
	Prodromal Effects	Manifest-Illness Effects	Survival
75-150	Mild	Slight decrease in blood cell count	Virtually certain
150-300	Mild to moderate	Beginning symptoms of bone marrow damage	Probable (>90 percent)
300-530	Moderate	Moderate to severe bone marrow damage	Possible-- Bottom third of range: LD _{5/60} Middle third: LD _{10/60} Top third: LD _{50/60}
530-830	Severe	Severe bone marrow damage	Death within 3½-6 weeks-- Bottom half: LD _{90/60} Top half: LD _{99/60}
830-1100	Severe	Bone marrow pan- cytopenia and moderate in- testinal damage	Death within 2-3 weeks
1100-1500	Severe	Combined gastroin- testinal and bone marrow damage; hypotension	Death within 1-2½ weeks
1500-3000	Severe gastrointestinal damage Upper half of range: early transient incapacitation; gastrointestinal death		Death within 5-12 days
3000-4500	Gastrointestinal and cardio- vascular damage		Death within 2-5 days

reflect the combined effects of gastrointestinal and hemopoietic damage. Survival is almost impossible unless a compatible bone marrow transplant is available. Nearly everyone irradiated at this level suffers severe prodromal effects during the first day after exposure.

Injuries from doses of 1100 to 1500 rads (cGy) are similar to those in the foregoing dose ranges but much more severe due to greater depletion of bone marrow stem cells,^{*} greater gastrointestinal damage, and systemic complications. Early transient incapacitation has been observed in monkeys and may appear in man.[†] At 1500 to 3000 rads (cGy) early transient incapacitation may become more frequent.[‡] An early-postexposure renal failure was reported in this dose range.^{**} Death results in less than 2 weeks from gastrointestinal injury, complicated by bone marrow damage and concomitant cessation of granulocyte production.^{††} Above about 2000 rads (cGy), death may occur sooner from electrolyte imbalance and dehydration due to vomiting and diarrhea, especially in hot or humid conditions. Extremely severe gastrointestinal and cardiovascular damage causes death within 2 to 5 days after doses of 3000 to 4500 rads (cGy).^{‡‡}

POSTEXPOSURE TIME CORRELATIONS

The onset and duration of prodromal symptoms in relation to radiation dose was estimated primarily from accounts of accident victims and therapy patients. Data on the Japanese atom bomb survivors are inadequate for prodromal symptom-time correlations, as noted in Sec. 1. For manifest-illness hemopoietic depression, however, the Japanese data are more reliable, having been recorded at the time of occurrence.^{***}

^{*}References 7, 65.

[†]Reference 23.

[‡]Reference 23.

^{**}Reference 98.

^{††}Reference 65.

^{‡‡}Reference 68.

^{***}References 2, 29, 60, 81, 82, 101, 106.

DOSE RATES

It is well known from radiobiological research that tissue cells are affected differently by different radiation dose rates as well as by different total doses. The data in this report include a great variety of dose rates. Accident victims were exposed to many thousands of rads in a fraction of a second.* In contrast, patients undergoing total-body irradiation were exposed to 1 to 30 rads (cGy)/min over periods of minutes to hours. We considered whether an adjustment of the therapy data for a dose rate differential to develop typical symptom descriptions was needed.

Given the great differences in dose rate between accident victims and therapy patients, it might be expected that their prodromal symptoms would begin at different times. However, correlation of the onset time of prodromal symptoms with dose level (Fig. 1) shows no marked difference between the two groups.† As for therapy patients alone, radiation therapists and radiobiologists recently said they had found no evidence of earlier onset of worse nausea or vomiting with increasing dose rate in the therapeutic range indicated above.‡ It is believed, therefore, that for deriving typical acute response patterns for symptoms such as nausea, vomiting, and fatigability, data from therapy patients are directly applicable.

*References 69, 70, 89.

†Reasoning from two studies of accident victims (Refs. 29 and 73), one analyst has suggested that prodromal symptoms and hematological injury are less severe with small daily doses at low dose rates than single high-intensity doses of equal size (Ref. 61). However, the dose rates for those accidents [0.05 and 0.02 rads (cGy)/min] were considerably lower than even the dose rates in our therapy patient data.

‡References 40, 99.

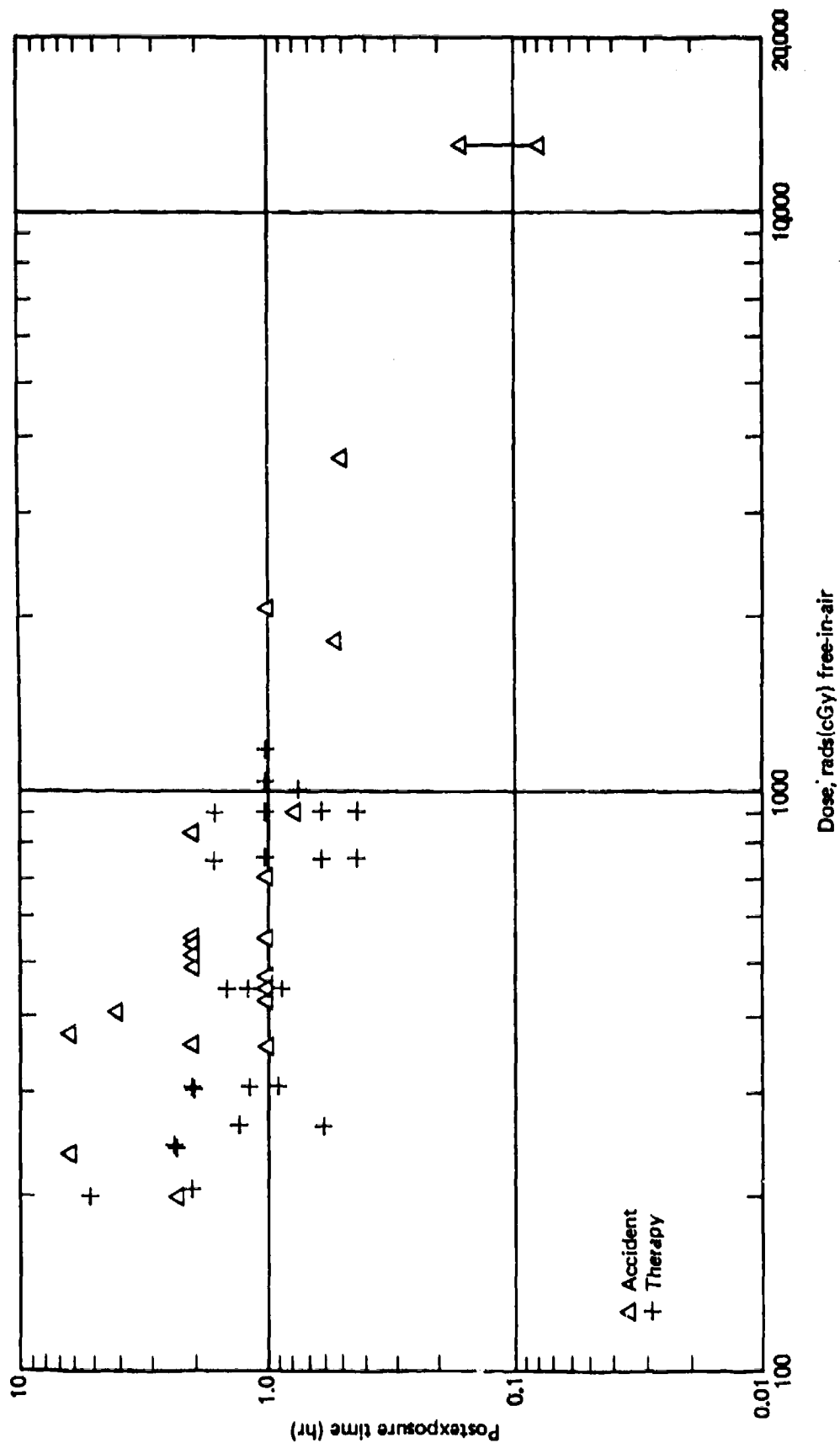


Figure 1. Onset of prodromal symptoms related to dose--data categories reflecting radically different dose rates.

SECTION 3

FINDINGS

This section sets forth descriptions of the typical course of radiation sickness for each of the eight dose ranges identified in Sec. 2. The descriptions are preceded by a discussion of our findings on the onset and duration of symptoms, symptom incidence, and radiation lethality.

ONSET AND DURATION OF SYMPTOMS

The onset of symptoms was estimated by plotting the relation between the time prodromal symptoms began and the dose (see Fig. 2). Logarithmic presentation is convenient because of the large range of actual doses--190 to 13,200 rads (cGy). Data points are indicated by symbols representing the four data categories:

<u>Category</u>	<u>References</u>
Accident (Δ)	30, 38, 52, 59, 62, 96, 105
Therapy (+)	17, 78, 88, 92
Composite (O)	42, 44, 46, 62, 69, 79, 110
Expert opinion (x)	9, 38, 42, 44, 46, 90, 96, 105

Where sources disagreed, we favored accident and therapy data over the other two categories. Each symbol indicates firm information; lines connecting the symbols indicate less certain ranges; arrows indicate open-ended values based on quite uncertain data.

Because the data vary greatly in density and precision, it was inappropriate to apply numerical techniques such as regression analysis. Instead, a curve was drawn through the data points to represent "typical" individuals. The curve shows onset time to be inversely proportional to dose.

The exact trend at the high end of the dose range is uncertain because of the lack of empirical data. However, the curve is supported by

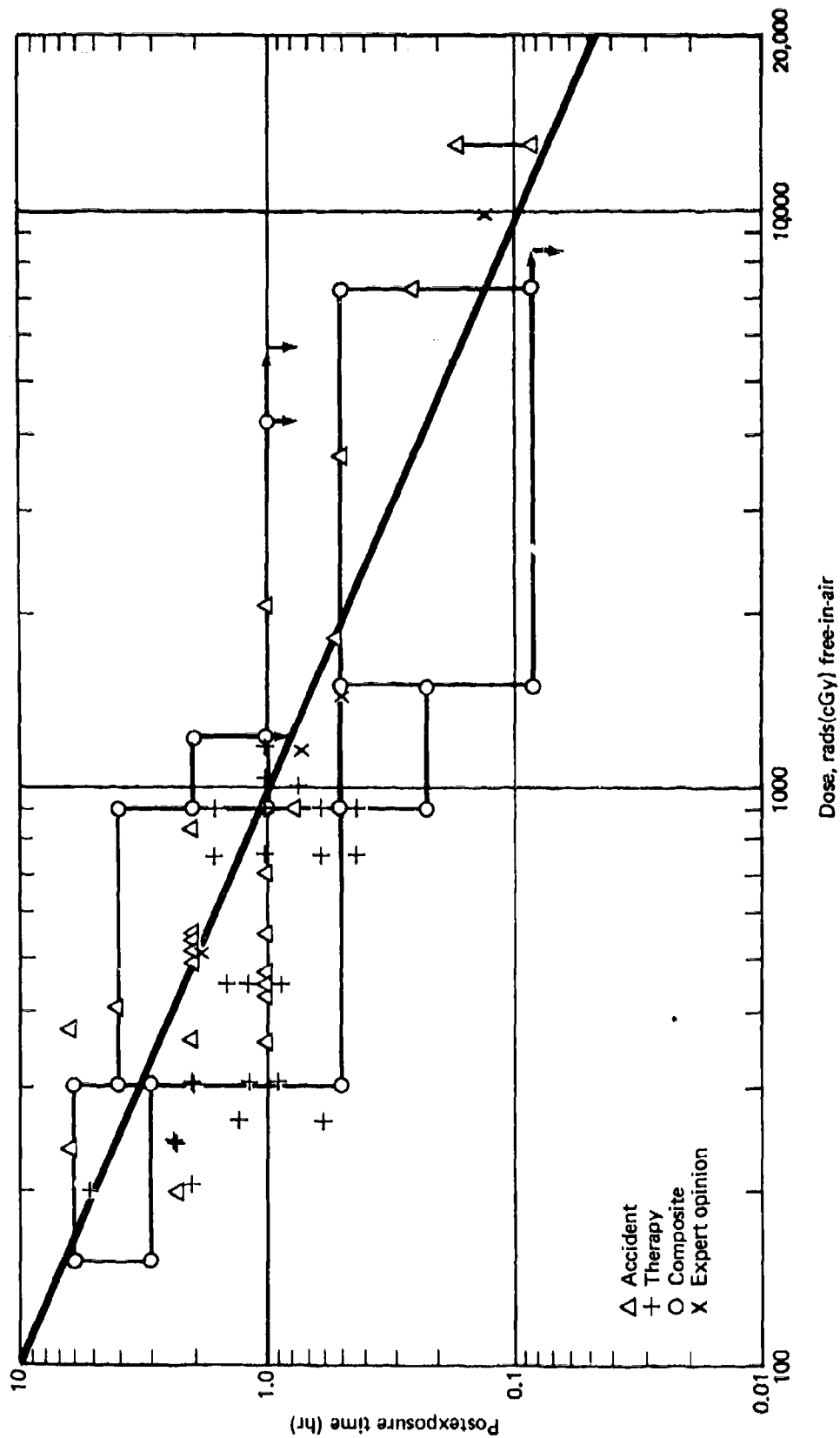


Figure 2. Onset of prodromal symptoms related to dose--all categories of data.

the accident data point at 13,200 rads (cGy)^{*} and by Langham's opinion that persons exposed to several thousand rads (MTD) will probably show the entire range of prodromal symptoms within 5 to 15 min.[†]

To check the representativeness of the curve, the temporal distribution of the onset of vomiting was examined in 100 male victims.[‡] The mean onset time was 144 ± 66 min after exposure to single doses above 450 rads (cGy). At 450 rads (cGy) the Fig. 2 curve corresponds to an onset time of about 2 hr, reasonably close to 144 min (2.4 hr), given the imprecision of the data. Moreover, with a standard deviation of ± 66 min (1.1 hr), and assuming an approximately normal distribution, prodromal symptom onset would be expected at 0.5 to 4.3 hr for 92 percent (i.e., 1.73σ) of those exposed. Indeed, the vomiting data and the curve are consistent with those confidence bounds.

To estimate the duration of symptoms in the prodromal and manifest-illness phases, we began with previously developed frameworks relating phase duration to dose.^{**} Deriving a consensus on symptoms from the data, we expanded the framework to specify the duration of each symptom identified in Sec. 2, related to dose.

INCIDENCE OF SYMPTOMS

Figure 3 shows the results of probit analyses relating the incidence of prodromal symptoms to radiation dose.^{††} Plotted on lognormal probability paper, the straight-line curves assume a lognormal distribution and the concave curves, a normal distribution.^{‡‡} The lognormal distribution generally fits the data better. Exceptions are the incidence of

^{*}Reference 59.

[†]Reference 61.

[‡]Reference 67.

^{**}References 9, 61.

^{††}References 61, 67, 69, 70, 105.

^{‡‡}Lognormal curves are based on data from accident victims and over 2000 therapy patients; normal curves are based on data from 163 therapy patients.

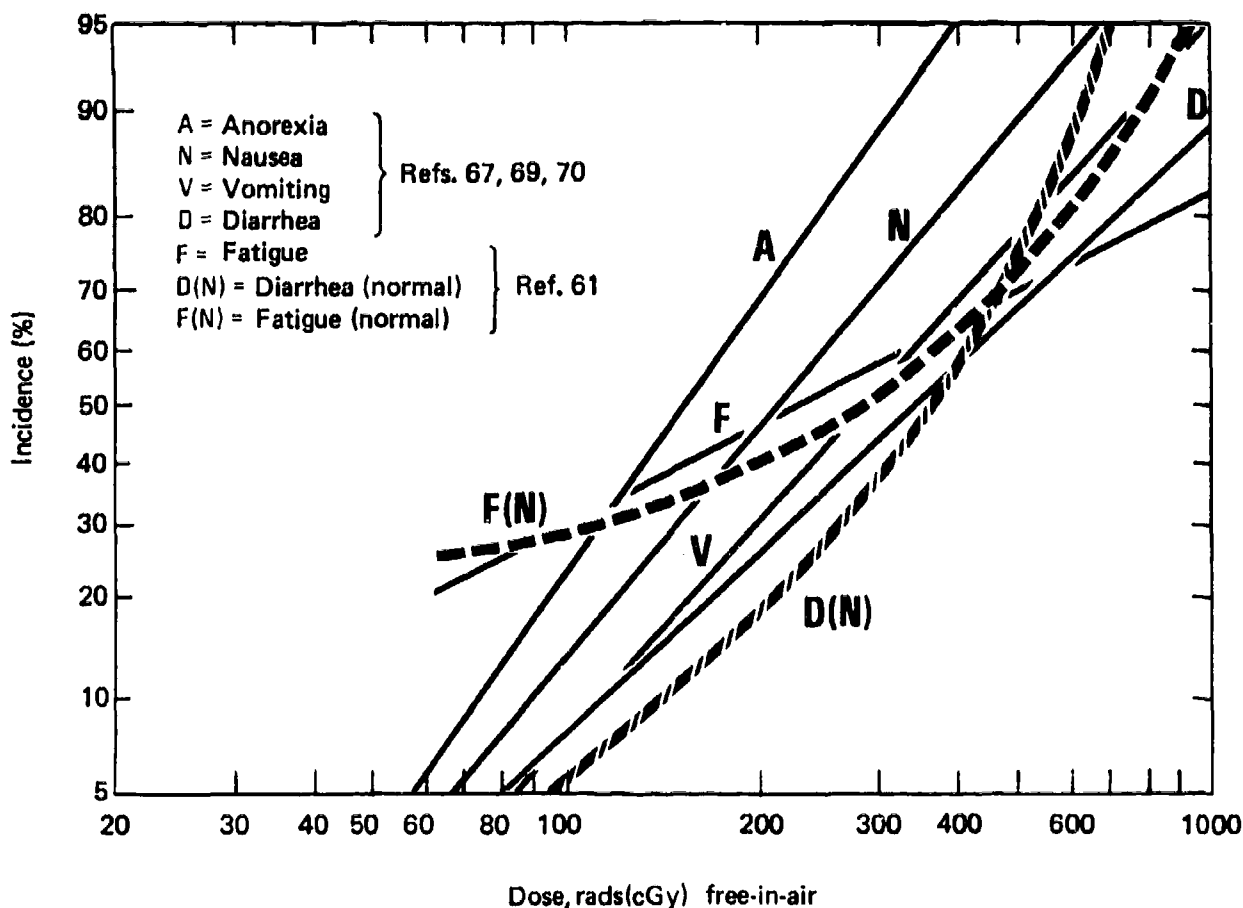


Figure 3. Symptom incidence related to dose (probit analyses).

fatigue at doses above 300 rads (cGy)* and the incidence of diarrhea at doses above 375 rads (cGy), for which the normal curves were used.

Qualification of the diarrhea data is in order. Unlike the other symptoms, diarrhea was monitored over a six-week period. Since the data are not time-resolved, the curves include later as well as early occurrences of diarrhea. In fact, other data suggest that these curves primarily reflect delayed diarrhea occurring a few days to a week after exposure. Early diarrhea is probably not manifested unless the dose is at least 450 rads (cGy). At that dose level, about 10 percent would

* Reference 61, Table 10, p. 82.

experience one or two episodes of diarrhea 3 to 6 hr after exposure; at doses of 3000 to 4500 rads (cGy), 30 percent could be affected.

RADIATION LETHALITY

Quantification of the incidence and postexposure time of death is uncertain because of the sparseness of human data. The three curves in Fig. 4 illustrate the uncertainty with respect to incidence: LD_{50/60} ranges from 400 to 525 rads (cGy). The right-hand curve was obtained by matching an estimate of 525 rads (cGy) for humans with an LD_{50/60} curve obtained from experiments with dogs.* The right-hand curve was used because lethality-dose curves tend to be parallel for large animals.

For time of death after radiation exposure, the ranges indicated by the heavily outlined boxes in Fig. 5 were used. As the various grids show, the boxes represent a consensus of fairly recent expert opinion and three fairly recent data points from human fatalities. For comparison a curve drawn through three earlier human data points is shown; the curve's shape is inferred from mammalian data. Relative to the curve, the boxes and the literature that support them show a trend toward earlier death with doses above ~2000 rads (cGy). That trend is also consistent with the fatality reported at 35 hr after a dose of about 7000 rads (cGy).† The plateau in the curve may misrepresent human lethality because of differences between the gastrointestinal systems of man and other mammals. The hemopoietic, gastrointestinal, and central nervous system notations at the bottom of the figure indicate the ranges at which those syndromes are the major contributing causes of death.

SYMPTOM DESCRIPTIONS

Descriptions of the symptoms likely to be observed in humans after exposure to ionizing radiation are presented for each of the eight dose ranges identified earlier. These descriptions, portrayed graphically and summarized in text, estimate symptom onset, severity, duration, and

*Reference 31.

†References 38, 59.

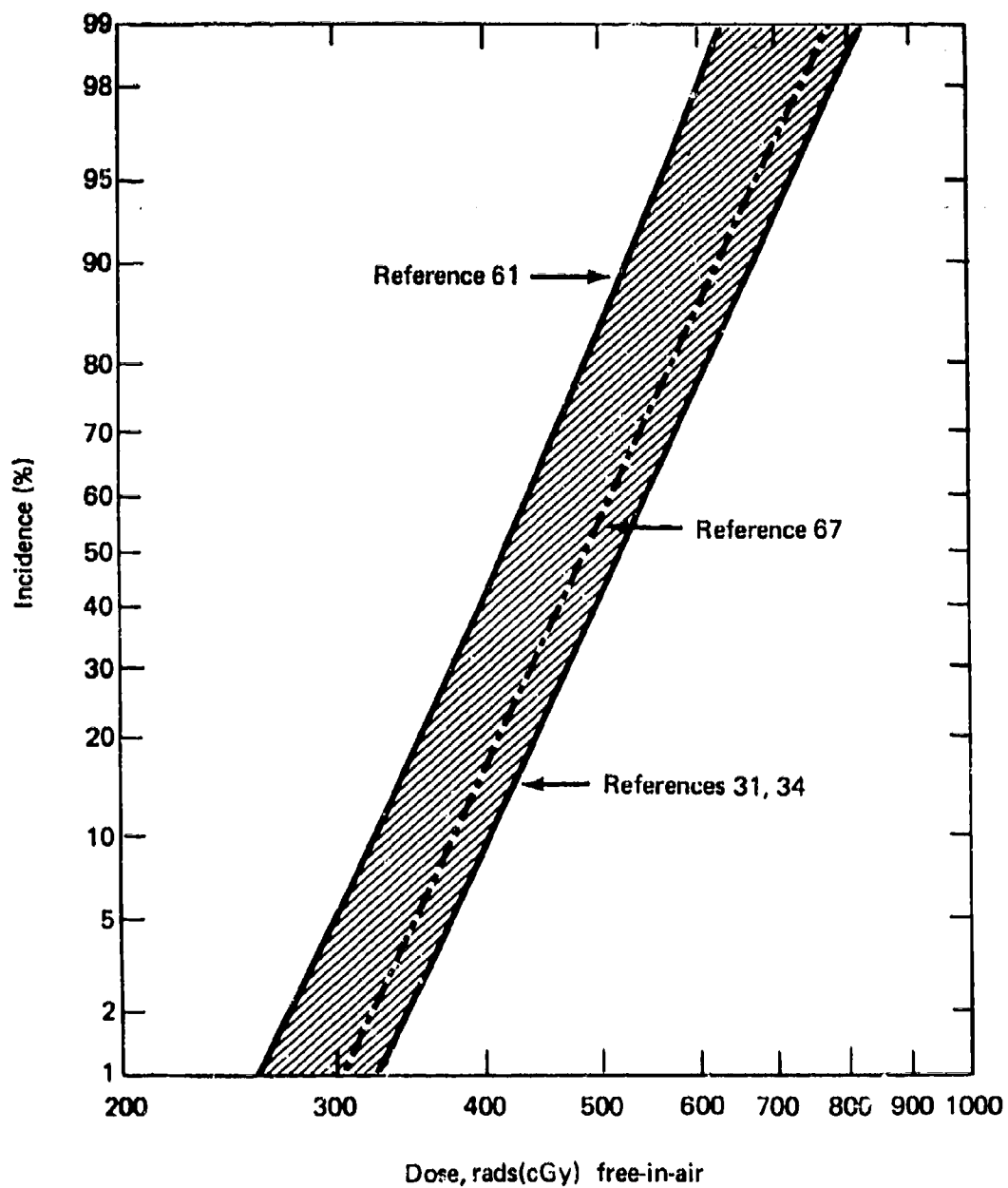


Figure 4. Lethality related to dose.

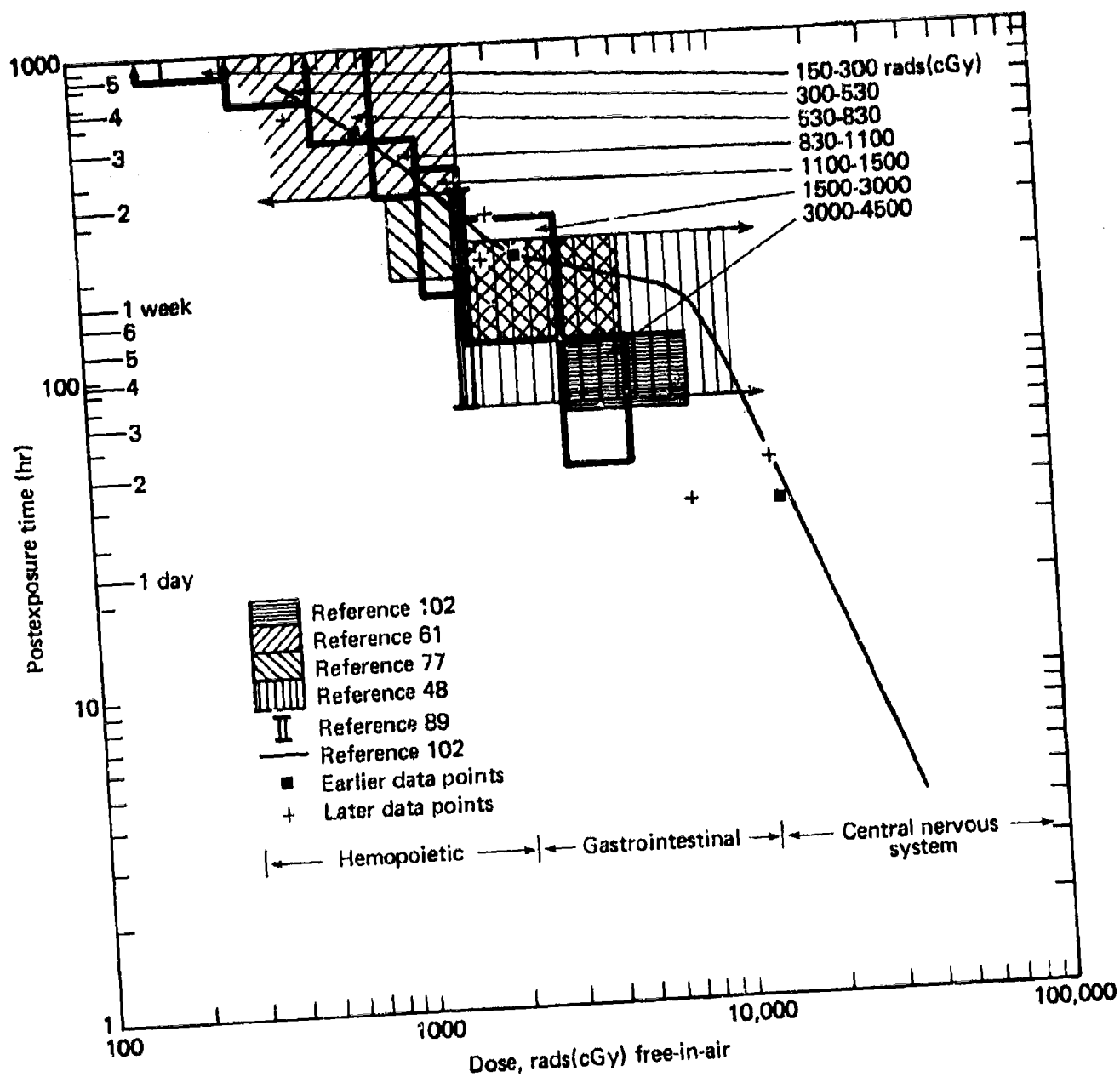


Figure 5. Time of death related to dose.

incidence. It should be reemphasized that a consensus was sought in the data, suppressing variability in order to represent the response of a typical exposed population.

Symptom incidence is expressed as a percentage range or single figure, depending on the firmness of the data. Estimates of the relation of symptom incidence with time are broad because of the lack of specific time-resolved data.

The estimates of duration imply that a symptom can occur one of three ways over the period indicated: continuously at one level of severity (e.g., anorexia); continuously with varying severity (e.g., fatigue^{*}); and intermittently (e.g., vomiting, diarrhea).

Quantification of the terms "mild," "moderate," and "severe" indicating symptom intensity is possible with only a few symptoms, as noted in Sec. 2.[†] Mild vomiting or diarrhea may mean a single to a few episodes during the period; moderate, several episodes; and severe, many and profuse episodes. Fatigue and weakness are potentially quantifiable since exertion, necessary to reveal those symptoms, is measurable;[‡] however, few data have been collected. With regard to hypotension, "mild" refers to a 10 percent drop in diastolic and systolic blood pressure; "moderate," a 10 to 30 percent drop; and "severe," a drop of 30 percent or more. Hemopoietic injury is quantified to the extent of estimating drops in platelet, granulocyte, and lymphocyte counts. Net continued fluid losses of up to 2 liters are considered mild to moderate; more than 2 liters, severe.

Regarding postexposure mortality, we estimate the incidence of fatalities and the period over which they are likely to occur for a given dose level. Data are insufficient to define a time distribution of mortality.

Doses of 75 to 150 Rads (cGy)

Table 2 indicates that acute radiation effects at this level are

^{*}Reference 21.

[†]Also, our correlations of severity level with time are gross representations; severity may vary considerably over time, as Gerstner's time-intensity profiles suggest (Refs. 41-43).

[‡]Reference 103.

Table 2. Symptoms for dose range 75 to 150 rads (cGy) free-in-air.

Symptom	Postexposure Time																							
	Hours								Days							Weeks								
	0	4	8	12	16	20	24		1	2	3	4	5	6	7	1	2	3	4	5	6			
Nausea ^a																								
Vomiting (retching)																								
Anorexia																								
Diarrhea (cramps)																								
Fatigue																								
Weakness																								
Hypotension																								
Dizziness																								
Disorientation																								
Bleeding ^b																								
Fever																								
Infection																								
Ulceration																								
Fluid loss/electro- lyte imbalance																								
Headache																								
Fainting																								
Prostration																								
Death																								

^aReferences for this group of symptoms: 1, 7, 15, 22, 26-30, 33, 37, 42, 50, 62, 66, 71, 72, 76, 78, 80, 85, 92, 96, 97, 105-107, 110, 111. These symptoms not observed in American servicemen exposed to approximately 78 rads (cGy) of fallout radiation, according to Refs. 26-29.

^bReferences for this group of symptoms: 1, 7, 14, 15, 26-30, 33, 50, 64, 72, 101, 105, 106, 108.

^cSlight drop in lymphocyte, platelet, and granulocyte counts; no overt symptoms.

mild and occur only during the first day after exposure. Blood cell counts may drop slightly, but typical victims will surely survive.

Doses of 150 to 300 Rads (cGy)

The severity of prodromal effects increases over the preceding range (Table 3). As the dose approaches 200 rads (cGy), 50 percent or more of exposed persons develop anorexia, nausea, and vomiting. About 30 to 60 percent complain of fatigue and weakness. Significant destruction of bone marrow stem cells may lead to a 25 to 35 percent drop in blood cell production. As a result, mild bleeding, fever, and infection may occur during the fourth and fifth postexposure weeks. Up to 5 percent may die 5 to 6 weeks after exposure to 300 rads (cGy).

Doses of 300 to 530 Rads (cGy)

Prodromal symptoms begin earlier and affect more exposed persons (Table 4). At this range and above, 10 percent may experience one or two episodes of moderate diarrhea 4 to 6 hr postexposure. Most victims tire easily and experience mild to moderate weakness intermittently over the 6 weeks. Under normal conditions, vomiting and diarrhea are not enough to cause serious fluid loss and electrolyte imbalance. In hot or humid conditions, however, combined fluid loss and electrolyte imbalance could become serious.

Injury to the hemopoietic system is indicated by moderate bleeding, fever, infection, and ulceration 3 to 5 weeks postexposure; more than 50 percent of those exposed are affected. During the fourth and fifth weeks, moderate diarrhea may complicate their condition. Five to 50 percent of nontreated persons may die during the fifth week; death comes earlier to those with preexisting infections, for example of the upper respiratory tract.

Doses of 530 to 830 Rads (cGy)

The onset and duration of nausea, vomiting, and anorexia are about the same as in the preceding dose range, but the symptoms are more severe and affect nearly all exposed persons (Table 5). Severe and prolonged vomiting takes a toll on electrolyte balance, which would be

Table 3. Symptoms for dose range 150 to 300 rads (cGy) free-in-air.

Symptom	Postexposure Time																				
	Hours								Days							Weeks					
	0	4	8	12	16	20	24	1	2	3	4	5	6	7	1	2	3	4	5	6	
Nausea ^a																					
Vomiting (retching)																					
Anorexia																					
Diarrhea (cramps) ^b																					
Fatigue ^c																					
Weakness																					
Hypotension																					
Dizziness																					
Disorientation																					
Bleeding ^d																					
Fever																					
Infection																					
Ulceration																					
Fluid loss/electrolyte imbalance																					
Headache																					
Fainting																					
Prostration																					
Death ^h																					

^aReferences for this group of symptoms: 4, 6, 7, 15, 17, 21, 22, 26-29, 33, 37, 42, 44, 45, 50, 51, 56, 62, 65, 66, 74, 76, 78-82, 85-87, 90-92, 95, 96, 104, 105, 107, 111.

^bTen percent of the Marshallese victims exposed to 175 rads (cGy) experienced diarrhea during the first postexposure day, according to Ref. 4.

^cReferences for this group of symptoms: 7, 50, 60, 65, 81, 85, 86, 90, 101, 102.

^dReferences for this group of symptoms: 6, 7, 14, 18, 21, 25, 26-29, 33, 35, 60, 62, 64, 65, 75, 76, 78, 79, 81, 82, 85, 89, 101, 104, 105, 107, 110.

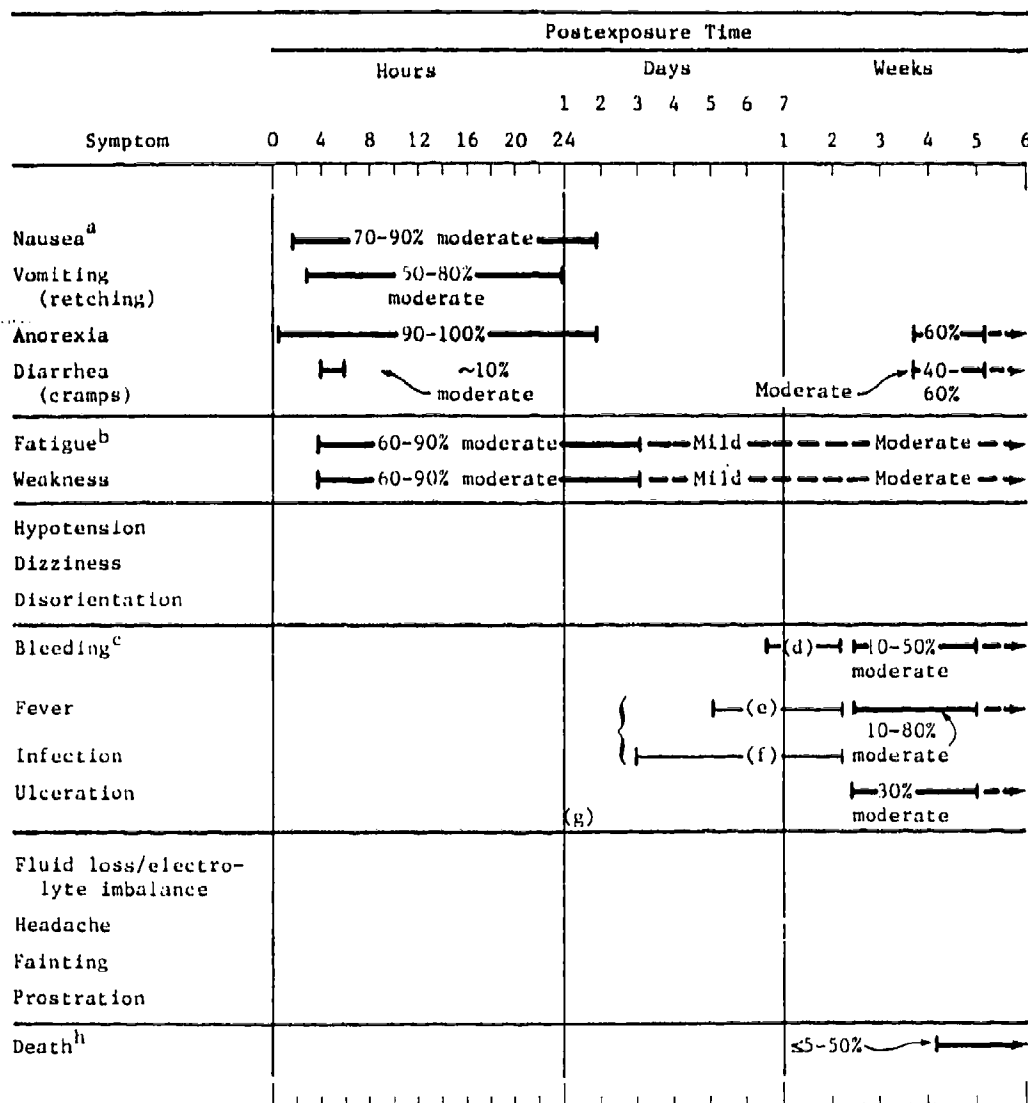
^eSlight to moderate drop in platelets: from $3 \times 10^5/\text{mm}^3$ to $1.8-0.8 \times 10^5/\text{mm}^3$.

^fSlight to moderate drop in granulocytes: from $6 \times 10^3/\text{mm}^3$ to $4.5-2.0 \times 10^3/\text{mm}^3$.

^gSlight to moderate drop in lymphocytes: from $3 \times 10^3/\text{mm}^3$ to $2.0-1.0 \times 10^3/\text{mm}^3$.

^hReferences for this event: 4, 14, 61, 81.

Table 4. Symptoms for dose range 300 to 530 rads (cGy) free-in-air.



^aReferences for this group of symptoms: 4, 6, 7, 12, 15, 18, 21, 22, 32, 33, 35, 37, 41-44, 47, 50, 51, 53, 56, 60, 62, 65, 75, 76, 80-82, 85-88, 90, 92, 95-97, 105-111.

^bReferences for this group of symptoms: 1, 7, 14, 43, 65, 71, 76, 81, 101, 104, 109, 110.

^cReferences for this group of symptoms: 2, 6, 7, 14, 15, 33, 35, 39, 54, 56, 60, 62, 64, 65, 71, 75, 76, 79, 81, 82, 85, 88, 95, 97, 101, 105, 106, 110.

^dModerate drop in platelets: from $3 \times 10^5/\text{mm}^3$ to $0.8-0.1 \times 10^5/\text{mm}^3$.

^eModerate drop in granulocytes: from $6 \times 10^3/\text{mm}^3$ to $2.0-0.5 \times 10^3/\text{mm}^3$.

^fModerate to severe drop in lymphocytes: from $3 \times 10^3/\text{mm}^3$ to $1.0-0.4 \times 10^3/\text{mm}^3$.

^gEpilation.

^hReferences for this event: 4, 7, 14, 61, 81.

Table 5. Symptoms for dose range 530 to 830 rads (cGy) free-in-air.

Symptom	Postexposure Time																									
	Hours								Days							Weeks										
	0	4	8	12	16	20	24		1	2	3	4	5	6	7	1	2	3	4	5	6					
Nausea ^a	90-100% severe moderate															60-100% moderate										
Vomiting (retching)	80-100% severe moderate																									
Anorexia	100%																	100%								
Diarrhea (cramps)	~10% moderate to severe															60-100% moderate to severe										
Fatigue ^b	90-100% moderate to severe																									
Weakness	90-100% moderate to severe																									
Hypotension ^c																										
Dizziness																Moderate		60%								
Disorientation																		60%								
Bleeding ^d																(e)		50-100% moderate to severe								
Fever																		(f)		80-100% moderate to severe						
Infection																		(g)								
Ulceration																				50% mild to moderate (h)						
Fluid loss/electrolyte imbalance ⁱ	50% mild to moderate																(j)									
Headache	50% mild to moderate																Moderate									
Fainting																	50%									
Prostration																	50%									
Death ^k																	50-99%									

^dReferences for this group of symptoms: 1, 4, 6, 7, 14, 15, 21, 22, 32, 33, 37, 41, 42, 50, 51, 53, 56, 58, 62, 76, 77, 79-82, 85, 87, 89, 90, 95-97, 101, 105, 106, 110, 111.

^bReferences for this group of symptoms: 1, 6, 7, 14, 47, 51, 53, 65, 78, 81, 85, 90, 101.

^cReferences for this group of symptoms: 77, 89.

^dReferences for this group of symptoms: 1, 6, 7, 14, 15, 18, 31, 33, 35, 54, 58, 62, 64, 65, 67, 71, 75, 76, 77, 81, 85, 90, 95, 101, 105-107, 110, 111.

^eSevere drop in platelets: from $3 \times 10^5/\text{mm}^3$ to $0.1 \times 10^5/\text{mm}^3$.

^fSevere drop in granulocytes: from $6 \times 10^3/\text{mm}^3$ to $0.5 \times 10^3/\text{mm}^3$.

^gSevere drop in lymphocytes: from $3 \times 10^3/\text{mm}^3$ to $0.4-0.1 \times 10^3/\text{mm}^3$.

^hEpilation.

ⁱReferences for this group of symptoms: 7, 14, 71, 81, 89, 101.

^jMild intestinal damage.

^kReferences for this event: 4, 14, 61, 81.

accelerated by perspiration loss through heat, humidity, or activity. About 10 percent may experience moderate to severe diarrhea 3 to 6 hr after exposure. Nearly all show moderate to severe fatigue and weakness for many weeks. If untreated, 50 to 99 percent may die, primarily because of extensive injury to the hemopoietic system, manifested in overwhelming infections and bleeding during the third to sixth weeks. Nausea, vomiting, and anorexia may recur at that time. Diarrhea, electrolyte imbalance, and headaches affect at least half. The condition of the lethally irradiated during their last days may be complicated by dizziness, disorientation, fainting, prostration, and symptoms of infection and bleeding.

Doses of 830 to 1100 Rads (cGy)

Virtually all exposed persons experience severe nausea and vomiting the first postexposure day, moderating over the next day or two (Table 6). During that time they also become dizzy and disoriented.

With the near-maximum destruction of bone marrow stem cells and absence of granulocytes, untreated persons lose their defense against infection. By the end of the first postexposure week, infection is rampant from endogenous bacteria that have escaped from the injured gastrointestinal tract.

The combination of hemopoietic damage and gastrointestinal lesions reduces the survival of all untreated persons to 2 to 3 weeks. During the entire time they suffer from severe fatigue and weakness. Toward the end of the first week, nausea, vomiting, and anorexia recur. Moderate to severe diarrhea may begin as early as the fourth day. Severe bleeding, headaches, hypotension, dehydration, electrolyte imbalance, and fainting complicate the condition of all during their last days.

Doses of 1100 to 1500 Rads (cGy)

The survival time for untreated persons diminishes to 2 to 2½ weeks (Table 7). Symptoms resemble those experienced at the preceding dose range, with the following notable differences:

Table 6. Symptoms for dose range 830 to 1100 rads (cGy) free-in-air.

Symptom	Postexposure Time																							
	Hours								Days							Weeks								
	0	4	8	12	16	20	24		1	2	3	4	5	6	7		1	2	3	4	5	6		
Nausea ^a	severe 100% moderate to severe															100% moderate to severe								
Vomiting (retching)	severe 100% moderate to severe															100% moderate to severe								
Anorexia	100%								100%															
Diarrhea (cramps)	10% moderate to severe								100% moderate to severe															
Fatigue ^b	100% severe															100% severe								
Weakness	100% severe															100% severe								
Hypotension ^c																100% severe								
Dizziness	100% severe															100% severe								
Disorientation	100% severe															100% severe								
Bleeding ^d									(e)							100% severe								
Fever									{ (f)							100% severe								
Infection									{ (g)															
Ulceration																(h) 100% severe								
Fluid loss/electrolyte imbalance ⁱ	80% moderate								{ (j)							80% moderate to severe								
Headache	80% moderate															100% moderate to severe								
Fainting																80% moderate to severe								
Prostration																								
Death ^k																100%								

^aReferences for this group of symptoms: 1, 4, 6, 7, 14, 15, 21, 22, 31, 32, 33, 41, 42, 44, 45, 47, 50, 51, 53, 57, 62, 65, 71, 76, 79-82, 85, 87, 90, 95-98, 101, 105, 106, 111.

^bReferences for this group of symptoms: 1, 6, 7, 14, 31, 47, 51, 53, 78, 81, 84, 90, 101.

^cReferences for this group of symptoms: 6, 7, 14, 15, 32, 33, 50, 61, 62, 65, 67, 71, 76, 85, 90, 95, 97, 101, 105, 106, 108.

^dReferences for this group of symptoms: 1, 6, 7, 12, 14, 15, 33, 35, 45, 58, 62, 64, 65, 67, 71, 75, 76, 79, 81, 85, 87, 90, 101, 105, 106.

^ePlatelet count drops nearly to zero.

^fGranulocyte count drops nearly to zero.

^gLymphocyte count drops nearly to zero.

^hEpilation.

ⁱReferences for this group of symptoms: 1, 6, 7, 12, 13, 14, 15, 33, 35, 62, 64, 65, 71, 75, 76, 79, 81, 85, 87, 90, 101, 105, 106.

^jModerate intestinal damage.

^kReferences for this event: 4, 14, 31, 61, 77, 81.

Table 7. Symptoms for dose range 1100 to 1500 rads (cGy) free-in-air.

Symptom	Postexposure Time																				
	Hours								Days							Weeks					
	0	4	8	12	16	20	24	1	2	3	4	5	6	7	1	2	3	4	5	6	
Nausea ^a	100% severe														100% moderate to severe						
Vomiting (retching)	100% severe														100% moderate to severe						
Anorexia	100%							100%													
Diarrhea (cramps)	10% severe							100% severe													
Fatigue ^b	100% severe														100%						
Weakness	100% severe														100%						
Hypotension ^c	~80% mild ^d														100% severe						
Dizziness	100% severe														100% severe						
Disorientation	100% severe														100% severe						
Bleeding ^e								(f)							100% severe						
Fever	~30-45% moderate ^d							{ (g)							100% severe						
Infection								{ (h)													
Ulceration															{ (i) 100% severe						
Fluid loss/electrolyte imbalance ^j	100% moderate							{ (k)							100% severe						
Headache	100% moderate to severe														100% severe						
Fainting															{ 70% moderate to severe						
Prostration															{ 70% moderate to severe						
Death ^l															100%						

^aReferences for this group of symptoms: 6, 7, 14, 15, 21, 22, 33, 41, 44, 47, 50, 51, 53, 57, 62, 65, 71, 76, 79-82, 85, 87, 90, 93, 95, 96, 101, 106.

^bReferences for this group of symptoms: 1, 6, 7, 14, 32, 47, 51, 53, 65, 67, 78, 85, 101.

^cReferences for this group of symptoms: 6, 7, 14, 15, 33, 50, 61, 62, 65, 71, 76, 79, 80, 82, 85, 87, 89, 93, 101, 105, 106.

^dBlood pressure drops 25 percent; temperature increases to 102°F, according to Ref. 33.

^eReferences for this group of symptoms: 6, 7, 14, 15, 33, 50, 61, 62, 65, 71, 72, 76, 79-82, 85, 87, 89, 90, 93, 95, 101, 106.

^fPlatelet count drops to zero.

^gGranulocyte count drops to zero.

^hLymphocyte count drops to zero.

ⁱEpilation.

^jReferences for this group of symptoms: 6, 7, 14, 15, 33, 50, 61, 62, 65, 71, 72, 76, 79-82, 85, 89, 101, 106.

^kModerate to severe intestinal damage.

^lReferences for this event: 4, 14, 61, 77, 81.

- Severe nausea and vomiting may continue into the third day before moderating.
- During the first day, hypotension affects about 80 percent; moderate fever, 30 to 45 percent.
- Electrolyte imbalance is a persistent problem from the sixth hour on.
- All have moderate to severe headaches during the first day.
- Nearly three-quarters are prostrate before the end of the first week.

Much of the description of symptoms at this dose range derives from postexposure observations of patients treated with total-body irradiation for leukemia. There are undeniable difficulties in extrapolating from sick people under close medical attention to otherwise healthy young soldiers on the battlefield; those difficulties are discussed beginning on p. 35. Nevertheless, therapy patients constitute the only substantial number of irradiated persons whose reactions have been thoroughly documented, so their experience is relevant to this inquiry. The acute sequelae observed in therapy patients are detailed in Appendix B.

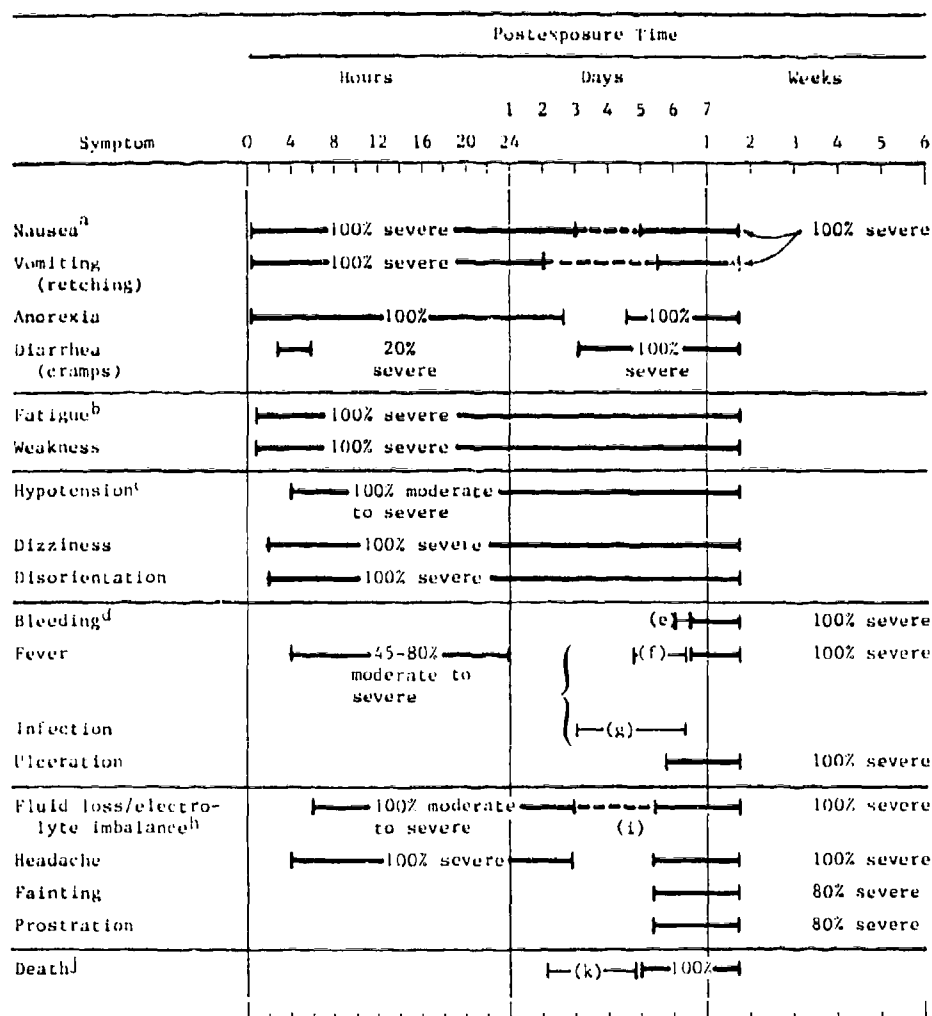
Doses of 1500 to 3000 Rads (cGy)

Severe nausea and vomiting affect all within 30 min of exposure and continue intermittently, along with anorexia, until death the second week (Table 8). Severe headaches begin after about 4 hr and continue for 2 to 3 days. Symptom severity may diminish somewhat during days 3 to 5. Gastrointestinal injury predominates, manifested 4 to 6 days after exposure by the abrupt return of severe nausea, vomiting, anorexia, and diarrhea, along with high fever, abdominal distension, and undetectable peristalsis (ileus).^{*} During the second week, severe dehydration, hemoconcentration, and circulatory collapse, compounded by septicemia, lead to coma and death.[†]

^{*}Reference 85.

[†]Reference 65. For more detail, see Appendix A.

Table 8. Symptoms for dose range 1500 to 3000 rads (cGy) free-in-air.



^aReferences for this group of symptoms: 6, 7, 14, 15, 21, 22, 31, 33, 47, 50, 62, 65, 67, 71, 76, 79-82, 85, 87, 90, 95, 101, 105, 106.

^bReferences for this group of symptoms: 6, 7, 14, 47, 53, 65, 71, 78, 85, 90, 101.

^cReferences for this group of symptoms: 6, 7, 14, 15, 33, 50, 61, 62, 65, 71, 76, 79-82, 85, 87, 89, 101, 105, 106.

^dReferences for this group of symptoms: 6, 7, 14, 15, 21, 22, 33, 47, 50, 62, 65, 67, 71, 76, 79-82, 85, 87, 90, 95, 101, 105, 106.

^ePlatelet count drops to zero.

^fGranulocyte count drops to zero.

^gLymphocyte count drops to zero.

^hReferences for this group of symptoms: 7, 14, 15, 33, 50, 61, 65, 68, 75, 76, 79-82, 85, 95, 101, 105, 106, 108.

ⁱSevere intestinal damage.

^jReferences for this event: 4, 14, 61, 81, 98.

^kRenal failure, according to Ref. 98.

Doses of 3000 to 4500 Rads (cGy)

Symptoms are more severe versions of those described for the preceding dose range (Table 9). Gastrointestinal injury predominates, complicated by cardiovascular lesions. Prodromal effects, including severe headache and drowsiness, appear almost immediately after exposure and may persist as the gastrointestinal syndrome develops. Severe dehydration and electrolyte imbalance are manifested several hours after exposure: initially fluids and electrolytes are lost by vomiting, but in time the greater loss is from severe diarrhea. The increased permeability of capillaries in the intestines and elsewhere in the body releases fluids into the interstitial spaces.*

APPLICABILITY OF TYPICAL SYMPTOM DESCRIPTIONS

Application of the estimates in Tables 2 through 9 to battlefield soldiers raises several questions because of the obvious differences in population characteristics, environmental conditions, and medical attention.

One question is whether the postexposure symptoms recorded for therapy patients could be distorted by the effects of their underlying disease and prior chemotherapy.

Another question pertains to the effects of postexposure medical care. Young soldiers trained for combat can generally be considered more robust than accident victims are before radiation exposure, and much more healthy than patients undergoing radiation therapy. Therefore, one might expect combat soldiers to better withstand the physical effects of ionizing radiation. However, all persons whose radiation response was examined in the data sources benefited from postexposure medical care, to which combat soldiers may not have access. Without such interventions as antibiotics and steroids, antiemetics, blood transfusions, intravenous fluids, bone marrow transplants, and bed rest, radiation sickness symptoms will be more widespread and severe, regardless of the individual's condition. The stresses engendered by nuclear war would of course compound the effects. Therefore, to what extent would the lack of medical care like that afforded

*References 68, 70, 85. For more detail, see Appendix A.

Table 9. Symptoms for dose range 3000 to 4500 rads (cGy) free-in-air.

Symptom	Postexposure Time																							
	Hours								Days							Weeks								
									1	2	3	4	5	6	7									
	0	4	8	12	16	20	24									1	2	3	4	5	6	7		
Nausea ^a	100% severe							100% severe																
Vomiting (retching)	100% severe							100% severe																
Anorexia	100%							100% severe																
Diarrhea (cramps)	~30% severe							100% severe																
Fatigue ^b	100% severe							100% severe																
Weakness	100% severe							100% severe																
Hypotension ^c	100% severe							100% severe																
Dizziness	100% severe							100% severe																
Disorientation	100% severe							100% severe																
Bleeding ^d																								
Fever	80-90% moderate to severe							{ (e) (f) }																
Infection								{ (f) }																
Ulceration																								
Fluid loss/electro- lyte imbalance ^g	100% severe							100% severe																
Headache	100% severe							100% severe																
Fainting ^h								100% severe																
Prostration								100% severe																
Death ^h								100%																

^aReferences for this group of symptoms: 6, 7, 14, 15, 21, 22, 42, 44, 50, 62, 65, 71, 76, 79-82, 85, 87, 90, 95, 101, 106, 108.

^bReferences for this group of symptoms: 6, 7, 14, 15, 21, 22, 50, 62, 65, 71, 76, 79-82, 85, 87, 90, 94, 95, 101, 105, 106, 108.

^cReferences for this group of symptoms: 14, 50, 61, 71, 76, 79, 80, 82, 85, 87, 94, 95, 101, 105, 108.

^dReferences for this group of symptoms: 7, 14, 50, 61, 71, 75, 76, 79-82, 85, 87, 94, 95, 101, 105, 106, 108.

^eGranulocyte count drops to zero.

^fLymphocyte count drops to zero.

^gReferences for this group of symptoms: 14, 15, 33, 50, 61, 62, 71, 75, 76, 79, 80, 82, 85, 87, 95, 101, 105, 108.

^hReferences for this event: 4, 14, 61, 77, 81.

accident victims and therapy patients be offset by the prior youth, vigor, and motivation expected in trained combat personnel?

Given the absence of relevant quantitative data, definitive answers are as yet impossible. Let us then consider the matter qualitatively.

Some have suggested that prodromal nausea, vomiting, fatigability, and diarrhea are partly psychogenic, so medical attention may be less effective in controlling them than in controlling purely somatic symptoms of hemopoietic or gastrointestinal damage.* Comparison of the experience of accident victims and therapy patients supports that assertion. When therapy patients received the best available antiemetic drugs before radiation, they showed similar patterns of early nausea and vomiting (incidence, severity, and duration) as accident victims exposed to comparable doses--even though the accident victims, of course, did not receive preirradiation antiemetics. The more recent introduction of steroid premedication in total-body radiation therapy markedly reduces the severity of prodromal effects.

Of particular relevance in contrasting hospital care with battle-field situations is the reduced availability of intravenous fluid replacement in the field. Without that replacement, fluid loss and electrolyte imbalance can be a life-threatening result of severe vomiting (with or without diarrhea) or sweating from exertion, particularly in hot, humid conditions. For example, heat stroke is much more likely if a person is dehydrated from vomiting.

Our general opinion is that preexposure health condition is less important than postexposure medical attention, barring prior bacterial or viral infection. Most experts would argue that, as dose increases beyond 300 rads (cGy) or so, any advantage gained through robustness will begin to be offset by the lack of medical care. As time increases past the first postexposure day, any such advantage would also diminish, given sublethal doses.

*The ability of medical care to counter later somatic damage is demonstrated by the effectiveness of current bone marrow transplantation procedures in preventing death from bone marrow suppression after radiation therapy.

With regard to dose, our symptom descriptions (based largely on the experience of persons who received medical care) are somewhat less applicable but still reasonably relevant to combat personnel exposed to doses at the lower end of our 75 to 4500 rad (cGy) range. The descriptions become increasingly applicable as dose increases.

With regard to postexposure time, prodromal symptoms are similar in both therapy patients (before steroids) and unmedicated accident victims. The descriptions of manifest-illness symptoms draw mainly from the experience of accident victims and atomic bomb survivors. Therefore, the authors believe the estimates of symptom onset and duration given here apply reasonably well to battlefield personnel.

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Appendix A

PATHOPHYSIOLOGY OF RADIATION INJURY

This appendix supports and explains the findings reported in Sec. 3 by describing the pathophysiology of radiation injury. The acute period of injury is conventionally divided into prodromal and manifest-illness phases.

PRODROMAL PHASE

The initial or prodromal phase^{*} begins about 2 to 4 hr postexposure for doses of 300 to 530 rads (cGy). As dose increases, the phase begins progressively earlier, within minutes of exposure to 4500 rads (cGy). Stomach distress appears, followed by anorexia. Vomiting occurs, especially with doses above 300 rads (cGy). If vomiting is severe, it is often accompanied by extreme weakness, and loss of body fluids can present problems. Depending on the dose, nausea, vomiting, and anorexia continue for 8 to 16 hr, even up to 2 days. Psychogenic factors may complicate the picture.[†] At lower dose ranges, a feeling of well-being may arise 24 to 48 hr after exposure and last 1 to 2 weeks.[‡]

Basic pathophysiological mechanisms in the prodromal phase remain somewhat unclear. Several causal factors have been suggested, including direct radiation effects on the central and autonomic nervous systems, disturbance of the endocrine balance, and production of various toxic substances.^{**} Symptoms of listlessness and nausea imply that higher structures of the nervous system are involved. However, since adult nervous systems are radioresistant in our dose range of interest, indirect involvement through chemical mediators is suspected.^{††}

*References 6, 7, 22, 47, 67, 81, 85, 89.

†References 7, 22, 47, 81.

‡Reference 85.

**Reference 44.

††Reference 44.

Vomiting is a complicated reflex between the central and autonomic nervous systems. Integrated in the medulla oblongata, the reflex is initiated by chemicals transported in the blood, impulses carried by autonomic fibers from abdominal organs to the medullary center, and the higher brain structures, including the cortex.* Experiments by Chin and Wang identified the medulla's chemoreceptor trigger zone as the main source of postradiation nausea and vomiting.†

Thus, the prodromal gastrointestinal reaction, at least for doses up to 4500 rads (cGy), seems to result not from direct radiation effects on the nervous system but from chemical compounds acting mainly on the medullary trigger zone.‡ It is thought that those chemical compounds are released from damaged cells of primarily lymphoid and bone marrow tissues.** The cellular debris reaches a maximum at 8 to 12 hr post-exposure, and is cleared by fixed and free macrophages 24 to 48 hr post-exposure. It has been suggested that disintegration of the lymphoid tissue is a cause of all prodromal reactions.†† If so, phagocytic action may be largely responsible for limiting the duration of the prodromal phase for doses up to about 1500 rads (cGy). At doses of 1500 rads (cGy) and above, the metabolic breakdown of cells, proteins, and amino acids can release uric acid. Without the administration of intravenous fluids to maintain the proper pH level, uric acid crystals can precipitate in the urinary system.‡‡

MANIFEST-ILLNESS PHASE

The later or manifest-illness phase is dominated by the hemopoietic and gastrointestinal syndromes. Much higher doses are required to initiate the gastrointestinal syndrome than the hemopoietic syndrome, but when both are present the compounding effect can be severe.

*Reference 16.

†Reference 24.

‡References 24, 44.

**References 36, 44.

††Reference 44.

‡‡Reference 8.

Hemopoietic Syndrome

At doses below 1050 rads (cGy), the hemopoietic syndrome begins about 8 to 10 days postexposure with a serious drop in granulocyte and platelet counts.* Pancytopenia supervenes about 3 to 4 weeks later; it becomes complete at doses above 750 rads (cGy).† Purpura is evident, and bleeding may be uncontrolled, causing anemia. Fever, pulse rate, and respiratory rate rise, due to endogenous bacterial and mycotic infections. Infections become uncontrolled given the impaired granulocyte and antibody production.‡ If at least 10 percent of the bone marrow stem cells remain uninjured, recovery is possible; otherwise, death occurs within 4 to 6 weeks.**

The pathophysiology of the hemopoietic syndrome is fairly well understood.†† All functional blood cells derive from common stem cells in the bone marrow, which are extremely radiosensitive. Functional cells such as granulocytes and platelets have a lifespan of only a few days,‡‡ and adult cells outside the stem cell compartment cannot renew themselves. Therefore, when immature stem cells are destroyed, blood cell production plummets or stops. The dearth of granulocytes and platelets permits bleeding and ulceration, accompanied by fever and fatal infections.***

Gastrointestinal Syndrome

At doses above 1050 rads (cGy), injury to the gastrointestinal tract contributes increasingly to the severity of the manifest-illness phase.

Under normal conditions, the integrity of the intestinal mucosa prevents the substantial escape of bacteria into the bloodstream. The

*References 2, 4, 18, 35, 57, 64, 75, 76, 106.

†References 6, 7, 81.

‡References 30, 66, 111.

**References 7, 65, 81, 85.

††References 2, 4, 7, 11, 14, 18, 32, 33, 37, 62, 65, 75, 85, 95, 97.

‡‡References 11, 14, 41.

***References 1, 7, 81, 101.

few bacteria that do escape are soon inactivated by granulocytes or specific antibodies. The radiosensitive mucosal stem cells in the crypts have a rapid turnover rate,^{*} producing mature, nondividing, differentiated cells that migrate to form the functional mucosal lining. Having a lifetime of several days, those mature mucosal cells are progressively shed and not replaced when radiation kills the stem cells in the crypt. The result is breakdown of the mucosa and ulceration. As the mucosa breaks down, large amounts of bacteria can enter the bloodstream. They go unchallenged because of the curtailed production of granulocytes[†] in the wake of radiation-caused damage to the bone marrow, so fever and infections are a consequence.[‡]

Even below the lower dose threshold cited above, at doses of about 450 to 1200 rads (cGy), temporary injury to the tight junctions between epithelial cells of the mucosal lining can permit the discharge of large amounts of molecular pyrogenic bacterial endotoxins into the bloodstream.^{**} At doses of 1050 to 1500 rads (cGy), the epithelial lining is more extensively depleted, and death results from septicemia within 2 to 3 weeks.^{††}

With doses of about 1500 to 2250 rads (cGy), denudation of the mucosa, particularly in the small intestine, leads to septicemia from gram-negative bacteria entering the bloodstream.^{‡‡} Beginning at doses of about 1900 rads (cGy), the septicemia is complicated by dehydration and electrolyte imbalance,^{***} resulting from exudation through the extensively ulcerated intestinal mucosa. Nutrition is lost because of impaired intestinal absorption, and infections are uncontrolled because of the complete bone marrow aplasia and subsequent pancytopenia.^{†††}

*References 14, 85.

†References 7, 65, 107.

‡References 13, 85.

**Reference 16.

††References 42, 50, 65, 81.

‡‡References 14, 33, 85.

***References 31, 64, 85.

†††References 14, 85.

This condition develops over a few days. Symptoms may not become severe until about the third or fourth day, when injury to the bone marrow and gastrointestinal tract described above leads to septicemia, fluid and electrolyte loss, and gastrointestinal infection accompanied by fever. Cramping, abdominal pains, and diarrhea, which may become watery, become more frequent and severe over the next week,* followed by shock and death.

At doses of about 2250 rads (cGy) and above, severe dehydration and electrolyte imbalance are likely to cause death from shock even before septicemia develops.

*References 7, 33, 65, 82, 85, 86, 111.

Appendix B

ACUTE SEQUELAE OF RADIATION THERAPY

This appendix draws on clinical experience with radiation therapy patients over the course of a decade to summarize the side effects of total-body irradiation.* The patients were being treated for leukemia, aplastic anemia, and other diseases, and received doses equivalent to single high-dose-rate exposures of about 750 to 1000 rads (cGy).† That is a dose range about which there is a dearth of information in other data sources, including case studies of accident victims, atomic bomb survivors, and early radiation therapy patients.

SYMPTOMS

Shortly after exposure, most patients experienced nausea, emesis, chills, and fever. Those symptoms usually subsided within about 10 hr and disappeared within 24 hr except for nausea and anorexia, which might persist for days. Emesis was aggravated by movement and often occurred with little warning.

In the first few hours after exposure, some patients showed decreased blood pressure and increased pulse rate due to circulatory hypovolemia. There were reports of acute myocardial insufficiency and death in patients with a history of myocardial disease.

A painful mumps-like swelling of the parotid gland developed within a few hours of exposure. The pain usually subsided within 2 days, but the swelling sometimes persisted for several more days. Xerostomia (dry mouth) sometimes lasted a week or more. During that time the saliva was reduced in volume, was thicker, and felt ropy. A metallic taste might persist as long as the mouth remained dry. Reduced salivary secretion added to patients' disinterest in food.

*The text is taken from Ref. 9, Appendix B.

†Unless otherwise noted, doses in this appendix are absorbed mid-line tissue doses. To convert to free-in-air dose values, multiply by 1.5.

About 10 percent of the patients developed diarrhea soon after irradiation. More developed diarrhea 1 to 7 days after exposure. Fatigability during the first 24 hr might be related to fluid loss and electrolyte disturbance. Thereafter the patient might feel better temporarily, but usually after 3 or 4 days diarrhea developed. At the same time, a sense of easy fatigability, apparently unrelated to fluid and electrolyte changes, sometimes returned to become a major complaint.

The oropharyngeal mucosae became reddened and sore 1 to 3 days after exposure and subsequently ulcerated. The condition took about 3 weeks to disappear. About 75 percent of the patients developed oral infections, owing not only to the ulcerated mucosae but also to leukocytopenia and immunosuppression. These infections became apparent as soon as 3 days after irradiation. The most common were fungal (thrush), but bacterial and herpes infections were also seen. Bacterial infections would probably have been more common except that patients were given antibacterial drugs.

Bone marrow suppression was indicated by increased susceptibility to infections and bleeding (e.g., of the gums) several days after exposure. If the patient had a preexisting infection, however, total-body irradiation was usually fatal, sometimes during the first postexposure week. Bone marrow grafts did not help.

A generalized erythema appeared as soon as 1 day after irradiation though usually later. It persisted for as long as 2 weeks and was sometimes associated with perineal irritation and itchiness. Beginning to 10 days after exposure there was a temporary incomplete loss of hair.

Sweating appeared to decrease in some patients. Though that phenomenon has not been adequately investigated, we can make a few observations. Inhibition of sweating seems not to present a serious problem in usual X- or gamma-ray treatment. The energy of the beam is high enough to spare the skin, and only small surface areas are irradiated. Inhibition of sweating could be lethal if large single doses are delivered from sources that do not spare the skin. Electrons were used to treat the total skin surface of a group of patients with mycosis fungoides. Penetrating only ~1 cm below the skin, the electron radiation was equivalent

to a single acute dose of 1000 to 2000 rads (cGy). Patients experienced marked erythema, decreased sweating associated with a generalized burning sensation, and low tolerance to exercise with consequent risk of hyperthermia.

PROBLEMS IN ASSESSING SYMPTOMS

Advances in therapeutic methods have introduced multiple variables that complicate symptomatology assessment. Some side effects (e.g., oral mucosal) may be intensified by the prior administration of cytotoxic chemotherapy drugs. Acute side effects have been markedly alleviated by premedication with antiemetics, steroids, and intravenous fluids. Infections have been reduced by preradiation decontamination and by not treating patients having evidence of infection.

All patients undergoing total-body irradiation received postradiation bone marrow transplants and drugs to combat graft-versus-host disease (GVHD). Since the anti-GVHD drugs produce side effects similar to those induced by radiation, it is difficult to distinguish the radiation-unique effects.

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